

REMARKS

Claims 50-55 were pending in the application. Pursuant to the telephonic interview of September 23, 2004 between Examiner Hope Robinson, Supervisory Examiner Jon Weber, and Applicant's representatives Catharina Chin Eng and Ann Chen, and the telephonic interview of September 27, 2004 between Examiner Hope Robinson and Applicant's representatives Catharina Chin Eng and Ann Chen, claims 50 and 55 have been amended to clarify the presently claimed invention (see discussion in the Statement of Substance of Interview Under 37 C.F.R. § 1.133 filed on November 4, 2004, 8, incorporated by reference herein). Specifically, claim 50 has been amended to replace the phrase "polymer-containing matrix" with the phrase "polymer matrix," and claim 55 has been amended to replace the phrase "locally administering" with the phrase "release of the therapeutic agent from the dosage form." These amendments are fully supported by the specification as originally filed, and no new matter has been added. Applicant respectfully requests that the amendments and remarks made herein be entered into the record of the instant application.

I. THE CLAIM REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ("WRITTEN DESCRIPTION") SHOULD BE WITHDRAWN

Claims 50-55 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that the claims broadly read on any "therapeutic agents" which encompasses a large genus of inhibitors not contemplated or described by the claimed invention. For the following reasons, Applicant respectfully disagrees.

1. The Legal Standard

The test for sufficiency of written description is whether the disclosure of the application "reasonably conveys to the artisan that the inventor had possession" of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983); accord *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d. 1111, 1117 (Fed. Cir. 1991); see also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985). The criteria for determining sufficiency of written description is set forth in the Guidelines for Examination of Patent Applications

Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (the "Guidelines") (published in Volume 66, Number 4, pages 1099-1111 of the Federal Register on January 5, 2001), which specifies that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or [i] by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, [ii] by functional characteristics coupled with a known or disclosed correlation between function and structure, or [iii] by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).
Id. at page 1106, column 3, lines 13-29.

Where the specification discloses any relevant, identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under 35 U.S.C. § 112, first paragraph, is misplaced. *Id.*

2. The Pending Claims Comply With The Written Description Requirement

The specification clearly describes the subject matter of the pending claims in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Amended claim 50 recites a method for reducing restenosis following a vascular surgical procedure (*e.g.*, angioplasty) by locally administering to a human a biocompatible, non-biodegradable sustained release dosage form that comprises a cytostatic amount of a free therapeutic agent dispersed in a polymer matrix. Specifically, the therapeutic agent is an agent that (i) inhibits vascular smooth muscle cell migration, (ii) does not exhibit substantial cytotoxicity, and (iii) does not substantially inhibit protein synthesis.

The Examiner contends that the specification only discloses therapeutic agents such as taxol, taxotere, or protein kinases. Contrary to the Examiner's allegation, the specification discloses therapeutic agents other than taxol, taxotere, and protein kinase. For example, the specification teaches many different classes of therapeutic agents that may be useful in the presently claimed invention, *e.g.*, page 4, lines 32-34 (therapeutic agents that alter cellular metabolism, inhibit protein synthesis, cellular proliferation or cell migration); page 4, lines 34-36 (microtubule and microfilament inhibitors that affect morphology or increases in cell

volume); page 4, line 36 to page 5, line 1 (inhibitors of extracellular matrix synthesis or secretion); page 5, lines 6-7 (protein kinase inhibitors); page 5, lines 7-8 (TGF-beta activators or production stimulators); page 5, lines 10-11 (nitric oxide releasing compounds); page 5, lines 15-18 (therapeutic agents that inhibit the contraction or migration of smooth muscle cells and maintain an enlarged luminal area following, for example, angioplasty trauma); page 30, lines 30-34 (a "cytostatic agent"); page 30, line 35 to page 31, line 1 (an "anti-migratory agent"); page 31, lines 1-4 (a "cytoskeletal inhibitor" or "metabolic inhibitor"); page 31, lines 4-6 (an "anti-matrix agent"). Moreover, the specification teaches a number of preferred therapeutic agents, *e.g.*, page 5, lines 6-7 (staurosporin, suramin); page 5, lines 9-10 (tamoxifen, TGF-beta); page 5, line 11 (nitroglycerin); page 5, lines 14-15 (taxol, taxotere); page 5, lines 18-20 (cytochalasin B, cytochalasin C, cytochalasin D); page 7, lines 31-32 (roridin A, *Pseudomonas* exotoxin); page 8, line 5 (sphingosine); page 8, lines 11 (somatostatin, N-ethylmaleimide); page 31, line 8 to page 32, line 3 ("cytostatic agents"); page 32, lines 4-16 ("anti-migratory agents"); page 32, lines 17-20 ("cytoskeletal inhibitors"); page 32, line 21 to page 34, line 2 ("metabolic inhibitors"); and page 34, lines 3-17 ("anti-matrix agents").

Applicant submits that one skilled in the art, based on the disclosure of the specification, would recognize that Applicant was in possession of the genus of therapeutic agents that are useful in the presently claimed invention. An applicant can show possession of the claimed invention by describing the claimed invention with a relevant, identifying characteristic. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). In this application, the specification not only describes a representative number of species of the genus of therapeutic agents useful for the presently claimed invention, it also provides three functional characteristics of those therapeutic agents useful for the presently claimed invention, *i.e.*, (i) inhibits vascular smooth muscle cell migration, (ii) does not exhibit substantial cytotoxicity, and (iii) does not substantially inhibit protein synthesis

For the foregoing reasons, Applicant respectfully submits that the rejection is in error and should be withdrawn.

II. THE CLAIM REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, (“ENABLEMENT”) SHOULD BE WITHDRAWN

Claims 50-55 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification, while being enabling for a method of reducing restenosis by administering taxol, does not reasonably provide enablement for any therapeutic agent/inhibitor employed by the method. For the following reasons, Applicant respectfully disagrees.

As a preliminary matter, Applicant respectfully submits that a similar rejection was raised in the prior Office Action mailed January 28, 2004, and addressed in the Amendment Under 37 C.F.R. § 1.111 filed on June 22, 2004. It is Applicant’s understanding that the rejection was discussed and withdrawn by the Examiner during the telephonic interview of September 24, 2004. However, during a telephonic interview on June 9, 2006, the Examiner informed Applicant’s representative Ann Chen that the rejection has been reinstated by the Examiner’s new supervisor.

1. The Legal Standard

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describes (1) how to make and (2) how to use the invention. *See* MPEP § 2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int’l Trade Comm’n 1983).

By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 1392, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that are relevant in determining what constitutes undue experimentation as set forth by the Federal Circuit (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)) include: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims.” Any conclusion of non-enablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d 731, 740, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

The Patent Office must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. “When rejecting a claim under the enablement requirement of § 112, the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application...” *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Patent Office’s *prima facie* case should address each of the *Wands* factors since “[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others.” See MPEP § 2164.01(a), citing *Wands* at 1407. Where the Patent Office does not provide evidence regarding one or more *Wands* factors, Applicant presumes that such factors support the conclusion that the claims at issue are fully enabled.

2. The Pending Claims Comply With The Enablement Requirement

The instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation as explained below. In particular, Applicant submits that one skilled in the art can make and use the invention, including a cytostatic amount of a free therapeutic agent that inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, by using the teaching from the specification *coupled with* information known in the art.

Applicant submits that the Examiner has not made an enablement rejection over the method *as a whole*. “The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent.” See MPEP §2164 (emphasis added). The present claims require locally administering to a human a biocompatible, non-biodegradable sustained release dosage form comprising a cytostatic amount of a free therapeutic agent dispersed in a polymer matrix, said therapeutic agent inhibits vascular smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. Thus, the therapeutic agent is not just *any*

therapeutic agent/inhibitor as the Examiner alleges, but a therapeutic agent that (i) *inhibits vascular smooth muscle cell migration*, (ii) *does not exhibit substantial cytotoxicity*, and (iii) *does not substantially inhibit protein synthesis*.

The Examiner applied four *Wand* factors under the test for undue experimentation. First, the Examiner alleges that one of skill in the art would have to engage in undue experimentation to test all possible inhibitors to determine if they have the desired activity. In response, Applicant submits that based on the teachings of the specification and information known in the art, one skilled in the art would know how to determine whether a therapeutic agent inhibits smooth muscle cell migration (see, *e.g.*, page 16, lines 18-24; Example 11), how to determine whether a therapeutic agent does not exhibit substantial cytotoxicity (see, *e.g.*, page 35, lines 6-8; Example 8), and how to determine whether a therapeutic agent does not substantially inhibit protein synthesis (see, *e.g.*, page 34, lines 29-33; Example 8). It would be well within the abilities of the skilled artisan to be able to apply and monitor biological assays that measure smooth muscle cell migration, protein synthesis inhibition, and DNA synthesis inhibition. Applicant submits that although *some* experimentation might be necessary to practice the present invention, the quantity of experimentation necessary is not unduly burdensome to one of skill in the art. Enablement is not precluded even if *some* experimentation is necessary, as long as the amount of experimentation needed is not unduly extensive. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Thus, contrary to the Examiner's allegation, the determination of therapeutic agents useful in the claimed methods does not require *undue* experimentation.

Second, the Examiner alleges that no guidance is presented with regard to other members of the genus of therapeutic agents encompassed in the claims. Contrary to the Examiner's allegation, the specification is not absent in guidance or direction. As discussed above, the therapeutic agent is not just any therapeutic agent/inhibitor as the Examiner alleges, but a therapeutic agent that (i) inhibits vascular smooth muscle cell migration, (ii) does not exhibit substantial cytotoxicity, and (iii) does not substantially inhibit protein synthesis. The specification clearly teaches and fully describes a large number of therapeutic agents other than taxol, taxotere, and protein kinase (see, *e.g.*, page 4, line 32 to page 5, line 20; page 7, line 11 to page 8, line 14; page 17, line 13 to page 22, line 11; page 30, line 24 to page 36, line 27). The specification also clearly teaches and fully describes methods for

determining the functional characteristics of those therapeutic agents useful for the presently claimed invention, *i.e.*, (i) inhibits vascular smooth muscle cell migration, (ii) does not exhibit substantial cytotoxicity, and (iii) does not substantially inhibit protein synthesis.

In particular, the specification teaches the skilled artisan how to determine whether a therapeutic agent suppresses or inhibits vascular smooth muscle cell migration. For example, the specification teaches that migration of smooth muscle cells may be studied *in vitro* by following the motion of a cell from one location to another using time-lapse cinematography or a video recorder and manual counting of smooth muscle cell migration out of a defined area in the tissue culture over time (see page 16, lines 18-24). The extent of smooth muscle cell migration inhibition can be measured using scratch assays (see Example 11).

The specification additionally teaches the skilled artisan how to determine whether a therapeutic agent exhibit substantial cytotoxicity. For example, the specification teaches that therapeutic agents exert minimal cytotoxicity (*i.e.*, does not exhibit substantial cytotoxicity) at concentrations where significant DNA synthesis inhibition occurs (see page 35, lines 6-8). The level of DNA synthesis inhibition can be measured using the ³H-thymidine DNA synthesis inhibition assay (see Example 8).

Furthermore, the specification teaches the skilled artisan how to determine whether a therapeutic agent substantially inhibit protein synthesis. For example, the specification teaches that therapeutic agents exert minimum protein synthesis inhibition (*i.e.*, does not substantially inhibit protein synthesis) at concentrations that do not kill the target cells (see page 34, lines 29-33). The level of protein synthesis inhibition can be measured using the ³H-leucine protein inhibition assay (see Example 8).

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970) (emphasis added). Here, the specification not only provides an extensive list of therapeutic agents that may be useful in the claimed methods, but it also teaches how the skilled artisan how to identify which of those therapeutic agents inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. Applicant submits that the amount of direction and guidance presented in the specification is more than sufficient. As such, the teaching of the specification bears a reasonable correlation to the entire scope of the claim.

Third, the Examiner alleges that the working examples provided do not rectify the missing information in the instant specification pertaining to the claimed inhibitors. In particular, the Examiner alleges that the nature and properties of the claims are difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct all inhibitors of the claimed invention and examine the same for function.

The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Any conclusion of non-enablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d at 740, 8 U.S.P.Q.2d at 1407. The absence of an illustrative examples is not determinant on whether undue experimentation is required. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Nevertheless, Applicant submits that, contrary to the Examiner's allegation, the specification does indeed describes four specific examples of free therapeutic agents that are useful in the claimed method, *i.e.*, suramin, staurosporin, nitroglycerin, and cytochalasin B (see Example 8).

Finally, the Examiner alleges that the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan, and the guidance presented in the instant specification and the prior art of record, together, makes the specification non-enabling for one skilled in the art to make and use the claimed invention. As previously discussed, the therapeutic agent is not just *any* therapeutic agent/inhibitor as the Examiner alleges, but a therapeutic agent that (i) *inhibits vascular smooth muscle cell migration*, (ii) *does not exhibit substantial cytotoxicity*, and (iii) *does not substantially inhibit protein synthesis*. Applicant submits that when all of the *Wands* factors are considered, one of ordinary skill in the art can determine without undue experimentation those therapeutic agents and amount of the therapeutic agents that would be sufficient to produce the claimed effect (*i.e.*, reduce restenosis). First, the quantity of experimentation necessary is routine and not unduly extensive. Second, the amount of direction or guidance presented is sufficient. Third, the specification provides a number of working examples of the method of the present invention. Fourth, the state of the art for determining whether a therapeutic agent inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, and the dose at which a therapeutic agent is cytostatic

shows that the claims are enabled. Fifth, the relative skill of those in the art is high in terms of practicing and monitoring the molecular scratch assay, the ^3H -leucine protein synthesis inhibition assay, and the ^3H -thymidine DNA synthesis inhibition assay. Sixth, the art of determining whether a therapeutic agent inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis, and the dose at which a therapeutic agent is cytostatic are predictable in view of the specification and knowledge in the art. Finally, the breadth of the claims is reasonable and not overly broad.

Applicant submits that one of ordinary skill in the relevant art would know which therapeutic agents may be used in the claimed methods, *i.e.*, an agent that inhibits smooth muscle cell migration, does not exhibit substantial cytotoxicity, and does not substantially inhibit protein synthesis. Applicant also submits that one of ordinary skill in the relevant art would know how much of the therapeutic agent is a cytostatic amount, *i.e.*, the amount that exerts minimum effect on protein synthesis and relatively more effect on DNA synthesis inhibition. Accordingly, the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.

For the foregoing reasons, Applicant respectfully submits that the rejection is in error and should be withdrawn.

III. THE DOUBLE PATENTING REJECTION SHOULD BE WITHDRAWN

Claims 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 4-6, 8-9, 11-12, 17, 23-24, 26, and 43 of U.S. Patent No. 5,981,568; claims 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 and 10 of U.S. Patent No. 6,663,881; claims 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 7-11, and 13-28 of U.S. Patent No. 5,733,925; claims 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 8, 10-14, 16-17, 20, and 26 of U.S. Patent No. 6,074,659; and claims 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 3-5, 7-10, and 13 of U.S. Patent No. 6,268,390. While not agreeing with these rejections, Applicant submits herewith a Terminal Disclaimer with respect to U.S. Patent Nos. 5,981,568; 6,663,881; 5,733,925; 6,074,659; and

6,268,390, with the necessary fee. The double patenting rejections are believed to be obviated by said Terminal Disclaimer, and should be withdrawn.

IV. THE CLAIM REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, (“INDEFINITENESS”) SHOULD BE WITHDRAWN

Claim 55 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to set forth the subject matter, which applicant(s) regard as their invention. Specifically, the Examiner alleges that claim 55 lacks clear antecedent basis for the recitation of “locally administering occurs *during* or after the vascular procedure” because the intent of the method is to administer after the vascular procedure and not during.

Pursuant to the telephonic interviews of September 24, 2004 and September 27, 2004 between the Examiner and Applicant’s representatives, Applicant has amended claim 55 to clarify that the therapeutic agent is released from the dosage form during or after the vascular procedure. Applicant respectfully submit that one skilled in the art, when reading amended claim 55, would find the claim language neither unclear nor indefinite. As such, the rejection is obviated and should be withdrawn.

CONCLUSION

As all rejections are believed to be overcome, all claims are believed to be in condition for allowance. An early notice to that effect would be appreciated. Should the Examiner not agree with Applicant's position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application. No fee aside from the fees associated with the filing of the Terminal Disclaimer submitted herewith are believed to be due. If any other fees are due, please charge the required fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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Enclosures